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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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PEACOCK MYERS, P.C.
201 THIRD STREET, N.W.
SUITE 1340
ALBUQUERQUE, NM 87102

EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/567,876	TESFAIGZI ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *10-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *2/28/06* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed April 28, 2008. Currently, claims 1-19 are pending. Claims 10-19 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election without traverse of Group I, Claims 2-9 in the paper filed April 28, 2008 is acknowledged.

The applicant correctly acknowledges that 10-19 are withdrawn. Generic Claim 1 will be examined with Group I. In the event Claim 1 becomes allowable, the linked inventions will be considered.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. This application is a 371 of PCT/US04/26035, filed August 11, 2004 and claims benefit of 60/494,631, filed August 11, 2003.

Drawings

4. The drawings are acceptable.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to a method for determining susceptibility of an individual to a COPD comprising determining the presence of an exon 6 codon 279 SNP within MMP-9 wherein the 279 arginine polymorphism indicates susceptibility to COPD.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches the exon 6, codon 279 arginine mutation is found at rs2664538. The art indicates this nucleic acid mutation exists at G2660A.

Lose et al. (Thorax, Vol. 60, pages 623-628, 2005) teaches the MMP-9 Arg279Gln mutation was not associated with asthma or asthma severity (abstract, page 626, col. 1). As seen in Table 3, the Arg279Gln polymorphism frequencies are provided.

Ganter et al. (International J. of Immunogenetics, Vol. 32, pages 233-236, 2005) teaches an association study of polymorphisms with MMP-9 and bronchial asthma. Ganter teaches the R279Q polymorphism within the MMP-9 gene were not associated with asthma. Ganter further teaches that in haplotype analysis, no association was found with asthma.

Nakashima et al. (Biochemical and Biophysical Research Communications, Vol. 344, pages 300-307, 2006) teaches analysis of polymorphisms within MMP-9 with asthma. Nakashima investigates whether variants of MMP-9 were related to childhood atopic asthma in Japanese populations by resequencing the MMP-9 gene, carrying out linkage disequilibrium mapping and conducting an association study with regard to the LD pattern (page 301, col. 1). Nakashima teaches 4841 was in complete LD with 2660G>A (the instantly claimed polymorphism)(page 303, col. 1). Nakashima teaches that SNP 10, namely 4841 which is in complete LD with 2660, is not associated with childhood atopic asthma (page 304, Table 3).

Saitoh et al. (International J. of Molecular medicine, Vol. 17, pages 621, 626, 2006) teaches analysis of MMP variants in Japanese and Egyptian subjected. Saitoh illustrates different ethnic groups may have varying associations. For example, in Table III, it is seen the Japanese population demonstrated an association with 6727, whereas Egyptian populations failed to demonstrate an association. Thus, different populations appear to show varying associations with COPD.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches p-values are used to assess whether studies are "real" or "pure chance". Thisted (May 1998) discuss what a p-value is. Thisted states that the p-value is important to determining whether differences observed are "real". Thisted states that "it has become scientific convention to say that p-values exceeding 0.05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their affects" (page 5). Therefore, it is clear that significance in the form of a p-value helps to determine whether the analysis was due to chance alone or

demonstrates a difference between two groups.

Guidance in the Specification.

The specification provides no evidence that the broad scope of the claims may be used as broadly as claimed.

The specification teaches, COPD is a general term that includes several overlapping lung conditions that share the common functional problem of airflow limitation. Chronic *bronchitis*, one of these lung conditions, is defined clinically as chronic productive cough. *Emphysema*, which is defined pathologically, is determined functionally by the decrease in elastic recoil and the increased resistance in the airways. *Asthma* with fixed airflow obstruction is included in the American Thoracic Society (ATS) definition of CO, PD and may be characterized as obstruction with a large reversible component although there is no clear recommendation of the degree of reversibility (page 2, lines 3-10).

The specification teaches a higher prevalence of the 279Arg homozygote genotype and the heterozygote genotype was seen in participants with COPD compared to non-COPD patients. The specification teaches the trend was not significant in Hispanic participants page 30, lines 6-7). The specification further teaches that no statistical differences in distribution for any of the genotypes were observed between COPD and non-COPD participates in the Women's Cohort (page 30, lines 8-10).

Table 3 illustrates that the herterozygosity in non-Hispanic white individuals is not associated with COPD, however, the rare homozygosity show a statistical significance with COPD. Table 3 illustrates that no significant association was found in Hispanics from the Veterans' cohort or any individuals from the Lovelace cohort. Table 4

illustrates that the Woman's cohort has no significant association with COPD. Table 4 also illustrates that Hispanic individuals failed to show an association with COPD.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to enable the skilled artisan to practice the claimed invention as broadly as claimed.

The claims are broadly drawn to any individual. Any individual encompasses not only humans, but also dogs and cats, for example. The specification fails to provide any analysis of dogs and cats. It is unclear whether the dog, for example has the 279 arginine mutation and whether the mutation is associated with COPD. The ordinary artisan would be required to perform significant further unpredictable and undue experimentation to determine whether the MMP-9 mutation is present in dogs and whether the mutation has any effect on COPD. Additional, individual encompasses any ethnicity, however the specification and the art illustrate that different ethnic groups have different patterns of association. The specification illustrates that the MMP-9 279 polymorphism is not statistically associated with COPD in Hispanic individuals. The art further teaches differences in association patterns in Japanese and Egyptian individuals. It is unpredictable whether a particular ethnicity is associated with COPD with out further unpredictable experimentation. It is trial and error experimentation to determine whether the mutation is associated with COPD in any particular ethnicity. Moreover, the specification demonstrates that in the Woman's cohort, there is not

statistical association with COPD and the mutation at 279. Thus, it is unpredictable, whether woman exhibit any association between COPD and the mutation at 279 and under what conditions.

The claims are broadly drawn to an association between a COPD and the presence of the 279 arginine polymorphism. The specification and the art teach a COPD encompasses bronchitis, emphysema, asthma, for example. Here, the specification teaches that heterozygous Gln279Arn was not associated with non-Hispanic white COPD whereas an association with rare homozygosity in non-Hispanic white was seen. Moreover, the art clearly teaches that the MMP-9 polymorphism at 279 is not associated with asthma in numerous post-filing date studies. While the skilled artisan could continue to perform additional experimentation to analyze the association of the 279 arginine polymorphism and any association with COPD, it is unpredictable whether any amount of experimentation would be able to replicate the instant analysis and association with a COPD. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art teaches the difficulties associated with association studies and phenotypes, it is unpredictable whether the skilled artisan could practice the broad scope of the instant claims. Further, the art and the specification provide insufficient guidance to overcome

the art recognized problems. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Conclusion

6. No claims allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner